Intensive care unit-acquired weakness: early diagnosis, symptomatology and prognosis
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CHAPTER 9

IMPACT OF ICU-ACQUIRED WEAKNESS ON POST-ICU MORTALITY AND PHYSICAL FUNCTIONING: A FOLLOW-UP STUDY

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Submitted
ABSTRACT

Objective
Intensive Care Unit – acquired weakness (ICU-AW) is thought to mediate physical impairments in survivors of critical illness but few studies have investigated this thoroughly. The purpose was to investigate differences in post-ICU mortality and physical functioning between patients with and without ICU-AW at 6 months after ICU discharge.

Methods
ICU patients, mechanically ventilated ≥2 days, were included in a single center prospective observational cohort study. ICU-AW was diagnosed when the average Medical Research Council (MRC) score was <4 in awake and attentive patients. Post-ICU mortality was recorded until 6 months after ICU discharge; in surviving patients physical functioning was assessed using the Short-Form Health Survey (SF-36) physical functioning (PF) domain. The independent effect of ICU-AW on post-ICU mortality was analyzed using a multivariable Cox proportional hazards model. The independent effect of ICU-AW on the PF domain score was analyzed using a multivariable linear regression model.

Results
156 patients were included, of whom 80 with ICU-AW. Twenty-three patients died in the ICU (20 with ICU-AW); during the 6 months follow-up after ICU discharge another 25 patients died (17 with ICU-AW). PF scores were available for 96 survivors (39 patients with ICU-AW). ICU-AW was independently associated with an increase in post-ICU mortality (HR 3.5 (95% CI: 1.3 to 9.4); p:0.01) and with a decrease in physical functioning (β: -16.7 points (95% CI: -30.1 to -3.3); p:0.02).

Conclusions
ICU-AW is independently associated with higher post-ICU mortality and with clinically relevant lower physical functioning in survivors at 6 months after ICU discharge.
INTRODUCTION

After surviving critical illness, many patients suffer from its long-term consequences, nowadays summarized as Post-Intensive Care Syndrome (PICS). PICS may consist of physical impairments, cognitive dysfunction, and mental health problems, and has a substantial impact on health care. The relevance of physical impairments in PICS was described in acute respiratory distress syndrome (ARDS) survivors, who continued to suffer from physical impairments up to 5 years after resolution of critical illness. It is thought that Intensive Care Unit-acquired weakness (ICU-AW) is an important mediator of physical impairments. However, evidence supporting this hypothesis is limited.

ICU-AW is a frequently occurring neuromuscular complication of critical illness, with an incidence of 46% (95% CI: 43-49) in patients with sepsis, prolonged mechanical ventilation or multiple organ dysfunction syndrome (MODS). In a cohort of acute lung injury (ALI) survivors, it was found that development of ICU-AW was associated with more physical impairments during follow-up. However, this association was not corrected for possible confounders. Also, ALI survivors represent a subgroup of critically ill patients and the association between ICU-AW and long-term physical impairments in critically ill patients in general remains to be investigated.

Besides being a possible mediator of post-ICU physical impairments, ICU-AW also has a substantial impact on post-ICU mortality. Two studies showed that ICU-AW is independently associated with increased in-hospital mortality. It is unknown if ICU-AW is also associated with mortality after hospital discharge.

In this 6-month follow-up study, we investigated the impact of ICU-AW on the post-ICU period by comparing post-ICU mortality and physical functioning between patients with and without ICU-AW. We hypothesized that ICU-AW is independently associated with an increase in post-ICU mortality and that survivors with ICU-AW have decreased physical functioning at 6 months after ICU discharge.

METHODS

Study design and ethical approval

We conducted a single center prospective observational cohort study. The institutional review board of the Academic Medical Center, Amsterdam, The Netherlands, decided that the study did not fulfill the criteria for medical research as stated in the Dutch ‘Law on medical research’ because the study was judged to be non-intrusive (METC 10/219). Still, we obtained verbal and/or written approval of all surviving patients.

Study setting

The study was performed in the closed-format tertiary 34-bed mixed medical-surgical Intensive Care Unit (ICU) of the Academic Medical Center in Amsterdam, The Netherlands. As an integral part of care, all patients received early rehabilitation that is continued after transfer to the regular ward until hospital discharge.
Study population
Inclusion criteria: newly admitted ICU patients aged ≥18 years, mechanically ventilated for ≥2 days. Exclusion criteria: neuromuscular disorder (e.g. Guillain-Barré syndrome), stroke, out of hospital cardiac arrest as reasons for admission and quadriplegia due to a spinal cord syndrome in medical history or as reason for admission. Additionally, we excluded patients in whom manual muscle strength could not be assessed because of prolonged delirium or failure to awake, patients who had poor functional status before admission (modified Rankin score ≥4) and patients with a language barrier.

Assessment of ICU-AW
ICU-AW was diagnosed using the current diagnostic reference standard. As a part of routine care, physical therapists performed manual muscle strength assessments using the Medical Research Council (MRC) score when patients were awake (Richmond Agitation Sedation Scale (RASS) between -1 and +1) and attentive (able to follow verbal commands using arms or eyelids). When assessed in awake and attentive patients, manual muscle strength assessment has good reliability. MRC scores of 6 different muscle groups were measured bilaterally: i.e. wrist dorsiflexors, elbow flexors, shoulder abductors, hip flexors, knee extensors and ankle dorsiflexors. MRC scores of muscle groups were summated and divided by the number of muscle groups that could be assessed to obtain an average MRC score (range 0 - 5). Symmetric weakness that had developed after ICU admission with an average MRC score <4 was defined as ICU-AW.

Mortality
All-cause mortality was registered during ICU-admission and in the 6 months follow-up after the final ICU discharge date. Mortality of patients who were lost to follow-up was obtained by checking municipal registries.

Physical functioning
Physical functioning was assessed in patients surviving to 6 months after the final ICU discharge date, using the Short-Form Health Survey (SF-36) physical functioning (PF) domain score. To optimize response rate, the SF-36 was assessed both by telephone interview and by mail.

Baseline and clinical characteristics
During admission, we scored the presence of the following disorders: sepsis, severe sepsis, septic shock and acute respiratory distress syndrome (ARDS). Additionally we collected the following characteristics from the electronic patient file: age, gender, body mass index (BMI; kg/m2), Charlson co-morbidity index, admission type, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score, maximal Sequential Organ Failure Assessment (SOFA) score during admission, days with mechanical ventilation, use of renal replacement therapy, ICU- and hospital length of stay.

Statistical analysis
The primary analyses were the independent effect of ICU-AW on post-ICU mortality and on the PF domain score. The independent effect of ICU-AW on post-ICU mortality was analyzed using
a Cox proportional hazard model (hazard ratio (HR) reported with 95% confidence interval) adjusted for confounders. Confounders were a priori defined as: age, gender, Charlson co-morbidity index, APACHE IV score and maximal SOFA score during admission. The independent effect of ICU-AW on the PF domain score was assessed using a multivariable linear regression model adjusted for the above-mentioned confounders (regression coefficient (β) reported with 95% confidence interval). A difference of 10 points on the PF domain score was defined as clinically relevant. The PF domain score assessed by telephone was used for analysis or, if unavailable, the PF domain score assessed by mail. Agreement between the two interview methods was assessed using the intra-class correlation coefficient (ICC reported with 95% confidence interval) in patients for whom both the telephone and mail PF domain scores were available. Because of the sample size, confounders for the multivariate models were summarized and entered as a propensity score. Assumptions of the different models (multicollinearity, normal distribution and proportionality of the hazard) were verified.

We also analyzed differences in the number of days free from hospital and alive at 3 months after the final ICU discharge between patients with and without ICU-AW using the Wilcoxon rank-sum test.

For descriptive analyses, mean values are presented with standard deviation (±SD), median values with interquartile range (IQR) and proportions with percentages and total numbers. Differences between proportions were assessed using chi-square test or Fisher’s exact test. Differences between normally distributed variables were assessed using Welch’s t-test; differences between non-normally distributed continuous variables were assessed using Wilcoxon rank-sum test.

A p-value less than 0.05 was considered statistically significant. Analyses were done using R (version: 3.0.1; R Foundation for Statistical Computing, Vienna, Austria).

**Sample size estimation**
This study was powered to detect a difference of 10 points on the PF domain score. With an alpha of 0.05, power of 80% and a common standard deviation of 10, 40 patients per group would be needed. Assuming that 50% of newly admitted ICU patients would develop ICU-AW, a mortality rate of 35% after 6 months follow-up, and that 10% of the population would be lost to follow-up, a population of 140 patients was needed.

**RESULTS**
Between May 2011 and January 2013, 156 patients were included of who 133 survived to ICU discharge. Figure 1 displays the study flowchart. Patient and admission characteristics are displayed in table 1.

**Post-ICU mortality**
Post-ICU mortality was higher in patients with ICU-AW (17/60 (28%) vs. 8/73 (11%); p<0.02). When adjusted for confounders, ICU-AW was associated with higher post-ICU mortality until 6 months after ICU discharge (HR 3.5 (95% CI: 1.3 to 9.4); p=0.01; 2 patients excluded because of missing APACHE IV scores). Figure 2 displays the post-ICU mortality curve. Most deaths
The number of days free from hospital and alive at 3 months after ICU discharge was lower for patients with ICU-AW (table 2).

Overall mortality, including the period of ICU admission, was 37/80 (46%) for patients with ICU-AW and 11/76 (15%) for patients without ICU-AW (p<0.01).
Table 1. Baseline and ICU admission characteristics for patients surviving to ICU discharge

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>ICU-AW (N:60)</th>
<th>no ICU-AW (N:73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>65 ±16</td>
<td>59 ±14</td>
<td>0.03</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>27 (45)</td>
<td>30 (41)</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (kg/m2), mean ± SD</td>
<td>26.8 ±5.1</td>
<td>26.9 ±5.2</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI &gt; 30, n (%)</td>
<td>14 (23)</td>
<td>16 (22)</td>
<td>1.00</td>
</tr>
<tr>
<td>Charlson co-morbidity index, median (IQR)</td>
<td>0 (0 to 1)</td>
<td>0 (0 to 2)</td>
<td>0.05</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ICU admission characteristics</th>
<th>ICU-AW</th>
<th>no ICU-AW</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission type</td>
<td>medical, n (%)</td>
<td>34 (63)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>surgical elective, n (%)</td>
<td>15 (21)</td>
<td>18 (24)</td>
</tr>
<tr>
<td></td>
<td>surgical emergency, n (%)</td>
<td>11 (16)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>APACHE IV score, mean ± SD</td>
<td>81 ±23</td>
<td>73 ±28</td>
<td>0.10</td>
</tr>
<tr>
<td>Maximal SOFA score during admission, mean ± SD</td>
<td>12 ±3</td>
<td>9 ±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sepsis during admission, n (%)</td>
<td>56 (93)</td>
<td>57 (78)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe sepsis during admission, n (%)</td>
<td>49 (82)</td>
<td>42 (58)</td>
<td>0.01</td>
</tr>
<tr>
<td>Septic shock during admission, n (%)</td>
<td>35 (58)</td>
<td>26 (36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal replacement therapy during admission, n (%)</td>
<td>23 (38)</td>
<td>19 (26)</td>
<td>0.18</td>
</tr>
<tr>
<td>ARDS during admission, n (%)</td>
<td>28 (47)</td>
<td>32 (44)</td>
<td>0.88</td>
</tr>
<tr>
<td>Days with mechanical ventilation, median (IQR)</td>
<td>11 (6 to 17)</td>
<td>5 (4 to 7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of stay in ICU (days), median (IQR)</td>
<td>14 (9 to 20)</td>
<td>7 (5 to 10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average MRC score, median (IQR)</td>
<td>2.8 (1.8 to 3.5)</td>
<td>4.7 (4 to 5)</td>
<td>n.a.</td>
</tr>
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</table>

<table>
<thead>
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<th>Post-ICU admission characteristics</th>
<th>ICU-AW</th>
<th>no ICU-AW</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days free from hospital and alive at 3 months after ICU discharge, median (IQR)</td>
<td>57 (15-71)</td>
<td>75 (56-82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Discharge destination from index hospital if discharged alive</td>
<td>other hospital, n/total n (%)</td>
<td>22/53 (41)</td>
<td>14/71 (20)</td>
</tr>
<tr>
<td></td>
<td>rehabilitation facility, n/total n (%)</td>
<td>14/53 (27)</td>
<td>4/71 (6)</td>
</tr>
<tr>
<td></td>
<td>home, n/total n (%)</td>
<td>17/53 (32)</td>
<td>53/71 (76)</td>
</tr>
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</table>

**Physical functioning**

Of the 108 patients who survived up to 6 months after ICU discharge, physical functioning was assessed in 98 patients (10 were lost to follow-up; figure 1). Patients’ place of residence when physical functioning was assessed is shown in table 2. Sixty-six questionnaires completed via the telephone and 32 by mail were used for the analyses. The ICC between the telephone-obtained and mail-obtained PF scores was 0.88 (95% CI: 0.67 to 0.95; N:30). The physical functioning
domain score was significantly lower in patients with ICU-AW (table 2). After adjusting for confounders, ICU-AW was associated with a decrease of 16.7 points on the PF domain score (95% CI: -30.1 to -3.3; p:0.02; 2 patients excluded because of missing APACHE IV scores).

Figure 2. Post-ICU survival curves for patients with and without ICU-acquired weakness
Survival curves for patients with (black line) and without (grey line) Intensive Care Unit-acquired weakness starting at final ICU discharge until end of follow-up, i.e. 6 months after final ICU discharge. Dotted lines represent the 95% confidence interval; censored patients presented with +.
ICU-AW: Intensive Care Unit-acquired weakness

<table>
<thead>
<tr>
<th></th>
<th>ICU-AW</th>
<th>no ICU-AW</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Post-ICU mortality</td>
<td></td>
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</tr>
<tr>
<td>in-hospital, n/total n (%)</td>
<td>13/60 (22)</td>
<td>4/73 (5)</td>
<td>0.01</td>
</tr>
<tr>
<td>after hospital discharge, n/total n (%)</td>
<td>4/47 (9)</td>
<td>4/69 (6)</td>
<td>0.71</td>
</tr>
<tr>
<td>PF domain scores at 6 months follow-up, median (IQR; n)</td>
<td>45 (30-70; 39)</td>
<td>75 (50-90; 59)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients’ residence at 6 months follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital, n/total n (%)</td>
<td>0/39 (0)</td>
<td>4/59 (7)</td>
<td>0.01*</td>
</tr>
<tr>
<td>rehabilitation facility, n/total n (%)</td>
<td>4/39 (10)</td>
<td>0/59 (0)</td>
<td></td>
</tr>
<tr>
<td>home, n/total n (%)</td>
<td>35/39 (90)</td>
<td>55/59 (93)</td>
<td></td>
</tr>
</tbody>
</table>

*: overall p-value for comparison of all categories. ICU-AW: Intensive Care Unit – acquired weakness; PF: Short-Form Health Survey (SF-36) physical functioning domain score
DISCUSSION

The results from this study show that, when assessed at 6 months after ICU discharge, ICU-AW is independently associated with higher post-ICU mortality and with clinically relevant lower physical functioning in survivors.

We found no difference in mortality after hospital discharge. However it should be noted that, up to the point of hospital discharge, already 41% of patients with ICU-AW had died and the duration of hospital admission after ICU-discharge was much longer for patients with ICU-AW. Additionally, we found increased ICU- and in-hospital mortality in patients with ICU-AW, which has been reported earlier.\textsuperscript{6,7} Ali et al. reported a combined ICU- and in-hospital mortality of 31\% in patients with ICU-AW, compared to 6\% for patients without ICU-AW. Sharshar et al. reported similar mortality rates (31\% in patients with ICU-AW; 10\% in patients without ICU-AW). Compared to these studies, we found a higher combined ICU- and in-hospital mortality rate in ICU-AW patients (41\%), whereas mortality in patients without ICU-AW was similar (9\%). This difference may be explained by differences in case-mix and in- and exclusion criteria.

Increased mortality in ICU-AW may be a result of the prolonged duration of mechanical ventilation, ICU- and hospital admission; all of which may increase the risk of nosocomial infections. Indeed, Sharshar et al. found that infections were the cause of death in 52\% of patients with ICU-AW.\textsuperscript{7} Alternatively, increased mortality may be the results of autonomic dysfunction that may accompany ICU-AW.\textsuperscript{25} In critically ill patients in general, autonomic dysfunction is associated with increased mortality.\textsuperscript{26} More research is needed to establish reasons for and prevention of mortality in ICU-AW.

In surviving patients, we found that ICU-AW is independently associated with decreased physical functioning. While it was known that survivors with ICU-AW have physical impairments\textsuperscript{5,27–29}, our study now shows that, by comparing to critically ill patients without ICU-AW and by correcting for possible confounders, this is indeed an effect of ICU-AW and not of other consequences of critical illness. Moreover, the effect of ICU-AW is clinically relevant, shown by the difference of more than 10 points on the PF domain score.\textsuperscript{20–22}

ICU-AW may cause post-ICU physical impairments by various mechanisms. In ICU-AW muscle and/or nerve can be affected, both on a functional and structural level.\textsuperscript{9} Decreased excitability may cause muscle and nerve dysfunction and this may resolve quickly.\textsuperscript{30} In contrast, structural damage may result in long-term symptoms.\textsuperscript{30} Also, nerve involvement as compared to muscle involvement has been linked to worse outcome.\textsuperscript{28,31,32}

Our study has some limitations. Because of the single center design, our results may not be fully generalizable to other populations. Also, we did not use electrophysiological studies and muscle biopsies to differentiate between the underlying disorders causing ICU-AW. Three disorders can cause ICU-AW, i.e. critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness neuromyopathy (CINM).\textsuperscript{9} The impact for the patient of additional diagnostic information obtained by electrophysiology and muscle biopsy is unclear because this has not been studied extensively. Three small studies described a better outcome in CIM.
Conclusions

In patients mechanically ventilated for 2 days or more, development of ICU-AW was independently associated with increased post-ICU mortality and clinically relevant lower physical functioning at 6 months after discharge from the ICU. These findings implicate ICU-AW as an important mediator of physical impairments associated with PICS. As such, studies on prevention or treatment of ICU-AW are urgently needed.

Acknowledgements

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Disclosures

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Figure E1. Survival curves for patients with and without ICU-acquired weakness from initial ICU admission to 6 months after final ICU discharge.
Survival curves for patients with (black line) and without (grey line) Intensive Care Unit-acquired weakness (ICU-AW) starting at ICU admission until end of follow-up, i.e. 6 months after final ICU discharge. Dotted lines represent the 95% confidence interval; censored patients presented with +. Using a multivariate* Cox proportional hazards model, ICU-AW was independently associated with an increased risk of death from ICU admission until 6 months after final ICU discharge (hazard ratio 3.8 (95% confidence interval 1.8-8.3); p<0.01; 2 patients excluded because of missing APACHE IV scores).
*: corrected with a propensity score calculated using age, gender, Charlson co-morbidity index, maximal total SOFA score during admission and APACHE IV score
ICU-AW: Intensive Care Unit-acquired weakness
REFERENCES


